EuroIntervention

Detection of left main stem and three-vessel coronary artery disease by myocardial perfusion SPECT imaging

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KEYWORDS
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Abstract

Stress radionuclide myocardial perfusion single-photon emission computed tomography (SPECT) imaging (MPI) is a well-validated diagnostic procedure for the assessment of patients with suspected coronary artery disease (CAD). It has a high sensitivity for the detection of flow-limiting coronary stenosis and provides incremental prognostic information that contributes to risk stratification and guides clinical-decision making with regard to management and therapeutic interventions. The diagnostic accuracy and predictive value of MPI in patients with three-vessel and left main stem (LMS) disease is less well-documented. There is evidence suggesting that assessment of myocardial perfusion on MPI is less effective at identifying significant three-vessel CAD as well as LMS disease. This limitation can be overcome, to a certain extent, by incorporating other imaging findings as well as clinical and stress testing parameters that help identify individuals at an increased risk of adverse cardiac events and hence those with severe and extensive coronary disease. Quantification of myocardial perfusion reserve using currently available radiotracers as well as simultaneous non-invasive assessment of coronary anatomy and atheromatous plaque may enhance the diagnostic performance of MPI in this subset of high-risk patients.

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Introduction

Stress radionuclide myocardial perfusion single-photon emission computed tomography (SPECT) imaging (MPI) is a non-invasive diagnostic procedure with a high sensitivity for the detection of obstructive coronary artery disease (CAD).[1] It provides an estimate of the extent and severity of disease leading to inducible myocardial perfusion abnormalities, and of myocardial viability and hibernation in patients with ischaemic left ventricular dysfunction. In the diagnostic work-up of intermediate-risk patients with suspected CAD, the use of MPI as the gatekeeper to invasive coronary angiography has been demonstrated to be a cost-effective strategy with significantly lower diagnostic and two-year follow-up management costs and similar clinical outcome compared with direct referral to catheterisation.[2,3] In this setting, elective coronary angiography is reserved for patients with refractory symptoms or a high-risk MPI study.

The incremental prognostic value of MPI over clinical, stress testing and angiographic data has been documented extensively.[4,5] MPI is a robust prognostic tool that allows stratification of patients according to their risk of future ischaemic events. In general, patients with a normal MPI study have a low annual rate of hard cardiac events (i.e., cardiac death, non-fatal myocardial infarction) that is in the region of 0.6%.[6] Conversely, patients with an abnormal MPI study have a 12-fold higher event rate that varies according to the extent and severity of perfusion abnormality. Recent studies have also demonstrated that MPI is a valuable method for the assessment of the effectiveness of medical therapy and intervention by documenting the presence and extent of ischaemia.[7,8] An MPI-based ischaemic threshold has been identified above which treatment choice is likely to influence important clinical outcomes and prognosis.[7]

The role of MPI and its diagnostic and prognostic value are less well-established in certain patient populations including those with three-vessel CAD and left main stem (LMS) disease. This article provides an overview of the advantages and limitations of MPI using SPECT technique for the detection of extensive CAD, in particular three-vessel and LMS disease, and comments on strategies that may improve the detection and assessment of patients with multivessel CAD.

Detection of CAD by MPI

MPI should be part of a diagnostic strategy for the detection and characterisation of myocardial ischaemia in patients with suspected CAD and stable symptoms. Indeed, the use of functional testing of ischaemia is recommended to guide clinical decision-making with regard to the need for invasive coronary angiography and revascularisation.[9] Despite recommendations from existing guidelines, less than half of patients undergoing elective coronary percutaneous intervention have non-invasive testing of ischaemia before revascularisation.[10]

Because the validity of results is influenced by the prevalence of disease (Bayes' theorem), available diagnostic tests are most effective in populations with an intermediate pre-test probability of disease. MPI is therefore recommended in patients with an intermediate pre-test likelihood of angiographically significant CAD according to clinical algorithms that incorporate age, gender, symptoms and cardiovascular risk factors in their estimation of risk.[11] This is important because interpretation of MPI results, whether in daily practice or from clinical trials, must take into account the clinical context and the baseline risk of the individual or patient population. As for most diagnostic tests, a normal MPI study in a patient with a high pre-test probability of CAD should be interpreted with caution. This is particularly relevant to the assessment of patients with suspected extensive CAD and LMS involvement.

Invasive coronary angiography has traditionally been the reference standard against which MPI is compared for the detection of "significant" coronary artery stenosis. Understanding of the superiority of functional testing over anatomy makes comparison with angiography less relevant; however, such comparison is still used partly because of the close relationship between angiographic results and decision-making regarding coronary revascularisation. In this regard, several reports have consistently shown a high sensitivity of MPI for the detection of angiographically significant coronary obstruction (85-90%) while its specificity for ruling out significant stenosis is in the region of 75%.[1] The normalcy rate of MPI is in the region of 90%.[1]

The high sensitivity of MPI for the diagnosis of CAD is partly attributed to the ability of the technique to detect perfusion abnormalities that result from reduction in coronary vasodilator reserve, an early manifestation of atheromatous coronary obstruction. Abnormal coronary vasodilator reserve leads to heterogeneous distribution of radiotracer in the myocardium and consequently the appearance of perfusion abnormality on MPI.

The detection of abnormal perfusion by MPI relies on the assessment of the distribution of radiotracer activity in the myocardium in relation to regional blood flow at rest and during stress-induced hyperaemia. In SPECT imaging, count density of each pixel within the myocardium is scaled relative to the pixel with maximum counts in each set of tomographic projections. Hence, image interpretation by visual analysis provides information on relative rather than absolute perfusion in each region of the myocardium. Global but uniform reduction in coronary vasodilator reserve would result in homogeneous distribution of radiotracer activity and therefore the appearance of "normal" perfusion throughout the myocardium on MPI. In other words, coronary obstruction in all vascular territories would account for homogeneous radiotracer uptake despite global ischaemia. As a result, detection of flow-limiting three-vessel CAD as well as LMS disease would be limited as contrast image is reduced by uniform decrease in myocardial perfusion. Semi-quantification of radiotracer activity within the myocardium in relation to a normal patient database may be helpful.[12] More importantly, there are well-recognised non-perfusion markers of cardiac risk that may help identify patients with significant multivessel and LMS disease.

Detection of left main stem disease by MPI

Significant LMS disease is defined as a greater than or equal to 50% stenosis on X-ray coronary angiography. Disease of the LMS is found in approximately 4% of patients undergoing diagnostic coronary angiography although prevalence might be higher in family groups

due to familial aggregation.[13] CAD with LMS involvement places the individual at high-risk for adverse cardiac events as occlusion of the LMS may compromise blood flow to a large region of the myocardium. Indeed, the high risk of major cardiac events and lower survival rates among patients with untreated LMS stenoses has been documented in the past.[14] Consequently, revascularisation of patients with known LMS stenosis may be considered regardless of the presence of objective evidence of ischaemia.[15] In patients with suspected CAD, early detection of LMS involvement may have a significant impact on management and prognosis.

There is limited data on the diagnostic accuracy of MPI for the detection LMS stenosis. There is no typical MPI pattern for LMS disease although it is generally agreed that an inducible perfusion abnormality involving both the left anterior descending (LAD) and left circumflex (LCx) coronary artery territories is consistent with LMS stenosis. However, such an appearance is not specific for LMS disease, and it is seldom found in patients with documented significant LMS stenosis.[16,17] The latter can partly be explained by differences in the extent and site of stenosis. A significant proportion of LMS lesions are distal and may involve the bifurcation. This may have a differential effect on myocardial perfusion downstream the LAD and LCx coronary arteries resulting in underestimation of LMS disease. Moreover, LMS disease is often associated with disease in other coronary vessels. A myocardial perfusion abnormality consistent with LMS may become less apparent in the presence of flow-limiting stenosis in other vessels. The diagnosis of LMS stenosis by MPI therefore requires a high index of suspicion and in most cases it cannot be reached by interpretation of the perfusion data alone.

Berman and colleagues have recently demonstrated that assessment of myocardial perfusion alone underestimates the presence of significant LMS disease (≥50% stenosis).[17] With the use of both visual and automated quantification of myocardial perfusion, normal myocardial perfusion was found in approximately 13% of patients with angiographic LMS stenosis while a pattern of radiotracer distribution suggestive of LMS involvement was present in only 21% of patients. These results support early studies investigating the ability of MPI to detect LMS disease. In the majority of these studies, the diagnosis of LMS stenosis was based on interpretation of myocardial perfusion results alone. Although 92% of thallium-201 MPI scans were abnormal in patients with LMS disease, radiotracer distribution compatible with LMS involvement was present in only 13% of patients.[16] This was partly attributed to the fact that all patients with LMS disease had concomitant stenosis in the right coronary artery (RCA) or in the coronary arteries downstream from the LMS lesion.[16] According to these observations, the presence of any perfusion abnormality on MPI identifies most patients with LMS disease but when a perfusion pattern consistent with LMS stenosis is used as marker of disease, the sensitivity of MPI is unacceptably low. While the former criterion is non-specific and would result in large numbers of patients undergoing unnecessary coronary catheterisation, the latter would fail to identify a significant proportion of patients with high-risk LMS disease.

It has increasingly been recognised that several non-perfusion imaging findings contribute significantly to the perfusion data and allow the detection of patients with CAD who are at a high risk of future ischaemic events (Table 1). Among this, transient ischaemic dilation of the left ventricular cavity (TID) in response to exercise or pharmacological stress is a strong predictor of cardiac events.[18,19] TID is characterised by an apparent increase in left ventricular cavity size at stress relative to the resting images (Figure 1). This is likely the result of global subendocardial ischaemia and/or stress-induced left ventricular dysfunction.[19] Regardless of the underlying mechanism, TID is found in patients with a large ischaemic burden and extensive myocardium at risk and is a powerful correlate of multivessel CAD[19].

Table 1. Markers of extensive and severe coronary artery disease on myocardial perfusion SPECT imaging.

Perfusion
1. Myocardial perfusion abnormalities involving more than one coronary artery territory
2. Increased right ventricular myocardial radiotracer uptake
Non-perfusion
1. Transient ischaemic left ventricular dilation (TID)
2. Increased lung radiotracer uptake
3. Stress-induced global left ventricular dysfunction on ECG-Gated SPECT
4. Stress-induced regional wall motion abnormalities

TID can also be found in the presence of "normal" myocardial perfusion suggesting balanced ischaemia. Although it is highly specific for severe and extensive disease in CAD patients, TID has also been described in relation to other conditions including left ventricular hypertrophy[20]. Nonetheless, TID should alert to the presence of extensive and severe CAD even in the absence of concomitant myocardial perfusion abnormalities.

Increased lung uptake of radiotracer on stress MPI is another marker of adverse prognosis and is often associated with severe CAD.[21] It indicates raised pulmonary capillary wedge pressure and is expressed as the ratio between lung and heart radiotracer counts. A lung-to-heart counts ratio ≥0.50 identifies patients at a high risk

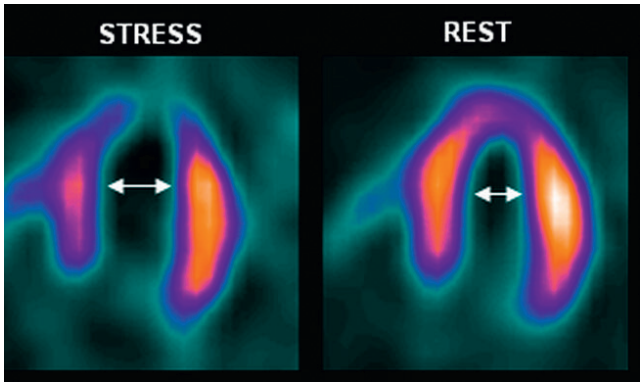

Figure 1. Transient ischaemic left ventricular dilation (TID) (arrows) on the horizontal long-axis views of a one-day adenosine/rest Tc-99m tetrofosmin MPI study of a patient with known three-vessel coronary artery disease. TID is commonly expressed as stress/rest left ventricular cavity volumes ratio and can be calculated using commercially available programmes.

for adverse cardiac events (Figure 2).[22] Although less well-documented, stress-induced increase in right ventricular radiotracer uptake relative to left ventricular uptake is associated with global left ventricular hypoperfusion and hence extensive and severe coronary disease (Figure 3).[23]

Most nuclear cardiology centres are now capable of simultaneous assessment of left ventricular function by ECG-gated SPECT of the stress and resting tomograms. Detection of global and regional abnormalities of contractile function adds incremental prognostic information to the perfusion data.[24] Left ventricular ejection fraction alone is a strong independent predictor of survival in patients with CAD.[25] In the detection of LMS and multivessel disease, a significant reduction in post-stress ejection fraction relative to resting function as well as new wall motion abnormalities may indicate extensive and profound ischaemia.[26,27]

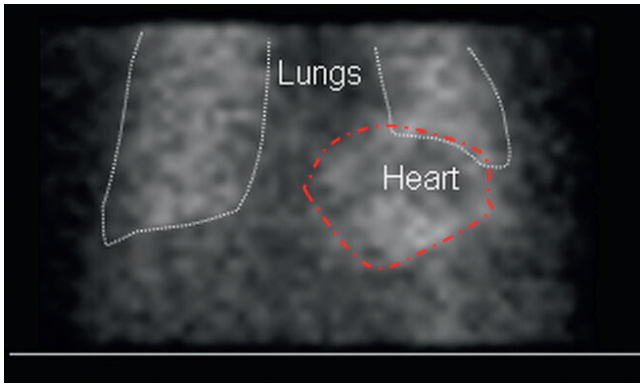

Figure 2. Increased lung uptake of thallium-201 (dashed lines) is identified on the stress raw data of a patient undergoing pre-operative cardiac risk assessment for orthopaedic surgery. Radiotracer lung uptake can be quantified and expressed as lung to heart counts ratio (L/H ratio). Values above 0.45-0.50 are considered abnormal.

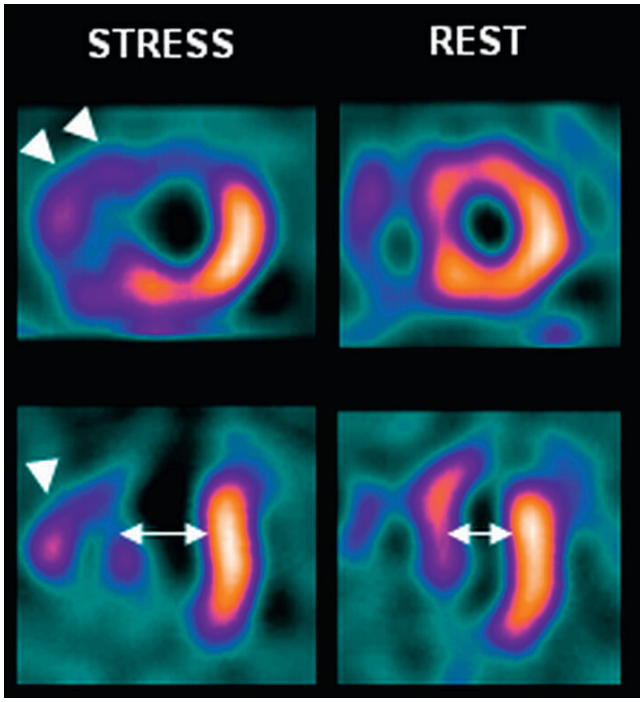

Figure 3. Stress/rest myocardial perfusion SPECT imaging in a patient with new onset chest pain. There is an extensive and profound inducible perfusion abnormality in the LAD territory and a mild abnormality in the inferior wall suggestive of possible RCA disease. Perfusion to the LCx territory appears normal. However, the increased right ventricular radiotracer uptake (arrowheads) together with transient ischaemic dilation (TID; arrows) strongly suggests the presence of multivessel disease with possible LMS involvement. The patient was found to have severe three-vessel disease with LAD occlusion on invasive coronary angiography.

When non-perfusion markers of extensive ischaemia are added to perfusion data, the proportion of patients with LMS stenosis identified by MPI increases (from 56% to 83%) (Figure 4).[17] This highlights the importance of image interpretation with careful consideration of non-perfusion markers of ischaemia. The presence of any of these markers should arouse suspicion of significant LMS disease (Figure 5).

There are other determinants of risk that should be considered in the diagnosis of LMS disease by MPI. In particular, the electrocardiographic and haemodynamic response to stress are important predictors of risk and significant CAD.[30,31] Patients with a normal myocardial perfusion scan but electrocardiographic ischaemia in response to vasodilator stress had a high risk of adverse events with an estimated non-fatal myocardial infarction rate of 7.6% over a 29-month follow-up period vs. 0.5% in patients with no ECG ischaemia.[30] Stress-induced hypotension and a low stress-to-rest heart rate ratio are also associated with significant disease and adverse prognosis.[31] Although these observations were not exclusive to patients with LMS disease, these factors contribute to the detection of patients at risk and may assist in the identification of a subset of patients with prognostically important LMS disease.

Detection of three-vessel coronary artery disease by MPI

Three-vessel CAD is present in about 9% of elective coronary angiograms.[32] As for LMS disease, significant three-vessel CAD is associated with a high incidence of adverse cardiac events and

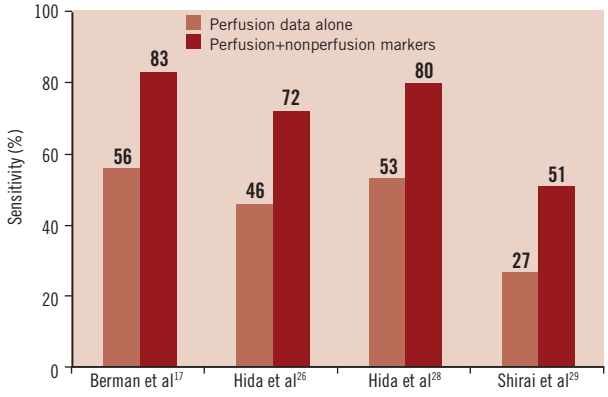

Figure 4. Sensitivity for the detection of extensive and severe coronary artery disease (multivessel CAD and/or left main stem disease) by myocardial perfusion SPECT imaging using perfusion data analysis alone vs. combined perfusion and non-perfusion markers of risk (references 17, 26, 28 and 29).

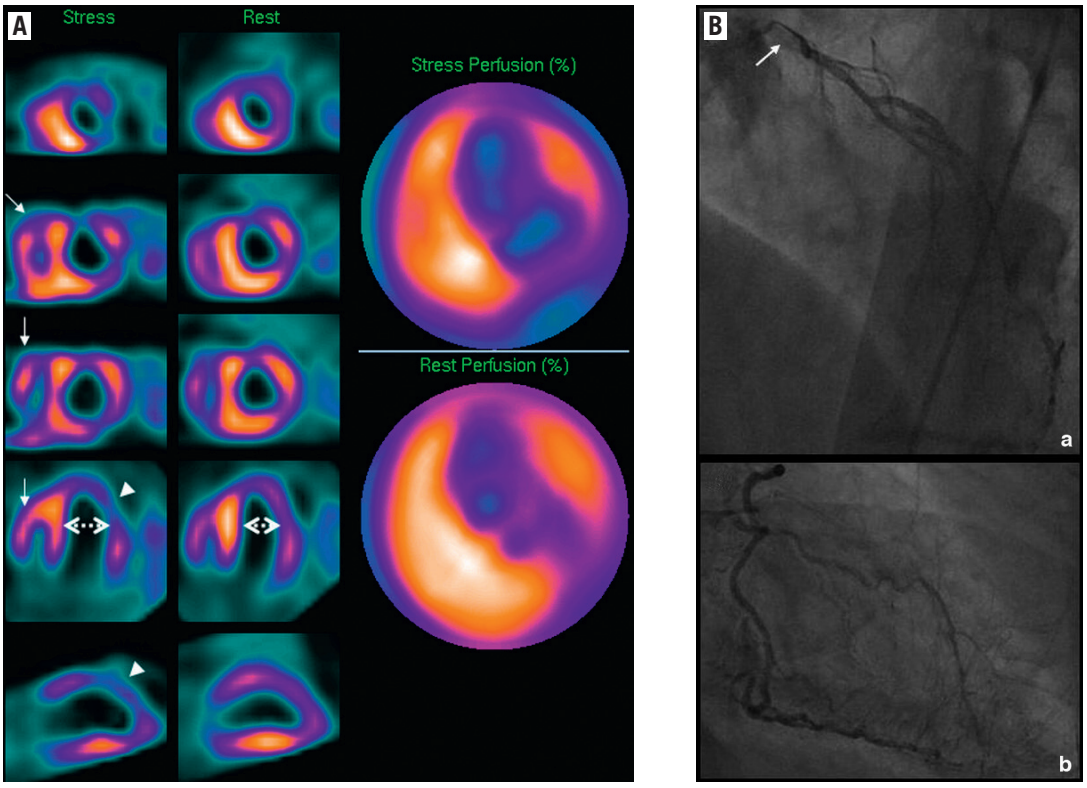

Figure 5. A) Adenosine/rest Tc-99m tetrofosmin myocardial perfusion SPECT study. The tomograms and the polar plots demonstrate a profound inducible perfusion abnormality involving both the left anterior descending (LAD) and the left circumflex (LCx) coronary artery territories (arrowheads) compatible with left main stem (LMS) stenosis. In addition, there is transient ischaemic dilation (TID; dashed arrows) and increased right ventricular tracer uptake (arrows). B) a: Coronary angiography reveals critical LMS stenosis (arrow) with proximal LAD occlusion. b: Unobstructed dominant right coronary artery with collateral vessels to the left coronary artery system.

hence early and accurate identification may lead to better outcome. In patients with known disease, clinical-decision making with regard to therapy and revascularisation would benefit from a reliable assessment of the functional significance of coronary stenoses.

MPI has a high sensitivity for the detection of CAD in patients with multivessel disease but accurate identification of patients with three-vessel involvement is limited.[33] Inducible perfusion abnormalities in all three coronary artery territories was identified in only 29% of patients with known angiographic three-vessel disease while another study reported a three-vessel disease pattern in 43% of patients.[34,35] A direct comparison with FFR measurements showed that MPI significantly underestimated the number of ischaemic myocardial territories as identified by FFR in patients with angiographic multivessel CAD.[33]

Although uncommon, balanced myocardial hypoperfusion or ischaemia in response to stress may result in apparently normal perfusion and underestimation of disease. In an unselected patient population with suspected CAD, only 1.1% had three-vessel and/or LMS disease and normal myocardial perfusion on MPI.[36] More often, underestimation of ischaemia in regions of the myocardium supplied by the least severe coronary stenoses results in one- or two-vessel rather three-vessel disease pattern on MPI. This may be explained by the kinetics of available radiotracers and the non-linear relationship between radiotracer uptake and absolute perfusion at high flow rates.[37] In addition, collateral circulation can maintain adequate perfusion to areas of myocardium supplied by a stenotic coronary artery leading to underestimation of the angiographic severity of epicardial lesion by perfusion imaging. From a diagnostic viewpoint, it may be less relevant whether the scan depicts a typical three-vessel disease pattern if there is myocardial ischaemia involving a significant proportion of total myocardium. A large ischaemic burden on MPI is associated with a high risk of ischaemic events and would support aggressive medical therapy and coronary angiography with a view to revascularisation.[7]

As for the assessment of patients with suspected LMS disease, incorporation of non-perfusion markers of risk adds diagnostic power to the perfusion data for the detection of extensive myocardial ischaemia and multivessel involvement.[28,29,38] Recent studies have demonstrated that an approach that combines dynamic changes in left ventricular volumes and function, perfusion analysis and clinical data enhances the prediction of three-vessel disease by MPI with a diagnostic sensitivity in the region of 72% and specificity 84%.[26]

Finally, it is important to recognise the contribution of clinical data to image interpretation. Clinical history plays a major role in daily practice but its contribution is seldom measured in studies. The incorporation of clinical information to non-invasive testing and imaging findings together with a multidisciplinary approach to patient management would prove the best strategy for the identification of patients at high-risk of ischaemic events among those with multivessel CAD and LMS disease.

Future directions

Advances in imaging technology may lead to superior image quality and may enhance diagnostic performance for the detection of multivessel and LMS disease.[39] Estimation of myocardial blood flow reserve using available radiotracers for SPECT imaging may contribute to the diagnosis of extensive CAD by depicting areas of myocardium with reduced flow reserve that may appear normal on visual analysis.[40] The contribution of absolute quantification of myocardial perfusion and estimation of flow reserve to the diagnosis of CAD has already been documented by studies using cardiac positron emission tomography (PET) imaging.[41] Noninvasive evaluation of coronary anatomy and coronary plaque characterisation by cardiac computed tomography (CT) in combination with functional assessment of coronary stenosis by MPI using SPECT/CT imaging may provide incremental diagnostic and prognostic information and contribute to the identification of patients at high risk of future ischaemic events among those with multivessel and LMS disease.

Conclusion

Identification of patients with multivessel CAD and LMS disease is of paramount importance as these patients are at an increased risk of adverse cardiac events and are more likely to benefit from coronary revascularisation, aggressive medical management and close monitoring. MPI is a robust noninvasive imaging technique for the detection of haemodynamically significant coronary stenosis that contributes to risk stratification of patients with suspected or known CAD. Assessment of myocardial perfusion alone may underestimate the presence of multivessel and LMS disease and hence all available information including non-perfusion markers of ischaemia, stress test results, and clinical history must be used to establish the presence and extent of disease. Functional assessment of coronary stenosis remains an essential investigation and should be used and interpreted appropriately within the clinical context.

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